UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,616	11/15/2005	Roy Curtiss III	56029-51044	4042

70119 7590 06/23/2010

THOMPSON COBURN LLP
ATTN: RICHARD E. HAFERKAMP
ONE U.S. BANK PLAZA
SAINT LOUIS, MO 63101

EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
06/23/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPDOCKET@THOMPSONCOBURN.COM

Office Action Summary	Application No.	Applicant(s)	
	10/511,616	CURTISS, ROY	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,9-11,21,26,31,32 and 34-40* is/are pending in the application.

4a) Of the above claim(s) *2,4,11,21 and 34-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,9,10,21,26,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/29/2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/29/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office Action is responsive to Applicant's amendment and response filed 3-29-10. Claims 1-2, 4, 9-11, 21, 26, 31-32, and 34-40 have been amended. Claims 3, 5-8, 12-20, 22-25, 27-30, and 33 are cancelled. Claims 1-2, 4, 9-11, 21, 26, 31-32, and 34-40 are pending. Claims 2, 4, 11, 21, and 34-40 are withdrawn from consideration. Claims 1-2, 9-10, 21, 26, and 31-32 are currently under examination.

Drawings

2. The corrected drawings replacing Figures 5/54, 6/54, and 7/54 filed on date 3/29/2010 in the present application has been accepted.

Information Disclosure Statement

3. The information disclosure statement filed on 3/29/2009 has been considered. An initialed copy is enclosed.

Rejections Withdrawn

4. In view of the Applicant's amendment and remark following rejections are withdrawn.

a) The rejection of claims 1, 5-6, 8-10, 26, and 31-32 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, regarding the word "means for regulatable", is withdrawn in light of applicant's amendment thereto and the cancellation of claims 5-6 and 8.

b) The rejection of claims 1, 5-6, 8-10, 26, and 31-32, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, reciting the phrases "first antigen", "first carbohydrate antigen" "second carbohydrate antigen", is withdrawn in light of applicant's amendment thereto and the cancellation of claims 5-6 and 8.

c) The rejection of claims 1, 5-6, 8-10, 26, and 31-32, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, reciting the phrase "ceases", is withdrawn in light of applicant's amendment thereto and the cancellation of claims 5-6 and 8.

d) The rejection of claims 1, 5-6, 8-10, 26, and 31-32, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, reciting the phrase "live attenuated derivative", is withdrawn in light of applicant's amendment thereto and the cancellation of claims 5-6 and 8.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

5. The rejection of claims 1-2, 9-10, 21, 26, and 31-32 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for the reasons set forth in the previous office action. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicants arguments filed in response to the 35 U.S.C. 112 first paragraph, March 29, 2010 is carefully considered, but not found to be persuasive for the reasons below.

Applicant argues:

A) Applicant respectfully notes that the claims as currently amended are drawn to "a regulatable $araCP_{BAD}$ promoter that is operably linked to a fur gene". As such, the Office's rejections of the claims as not teaching "any structural limitations of any regulators" (page 7 of the Office Action) are obviated with respect to item i) as the claims as currently amended recite a specific promoter. This specific $araCP_{BAD}$ promoter was known at the time of filing, structurally defined, and shown to function as per the claims in working examples provided by the Applicant. There is thus no reason to believe that one of ordinary skill in the art would doubt that the Applicant was in possession of the $araCP_{BAD}$ promoter.

B) Applicants state with respect to item ii) (i.e. "the genus of regulators capable a means of regulating synthesis for a first carbohydrate"), Applicant points to the disclosure of the specification on pages 18, 19, and 20 of the Application as filed that disclose regulators of LPS-O antigens and the claim amendments presented herewith that substitute "an LPS-O antigens" for "a first carbohydrate". More specifically, the specification discloses both mutations in or regulation of genes of the rfb gene cluster as well as mutations in the pmi gene that are suitable for regulating expression of LPS O-antigens. On page 20, the specification further indicates that such regulation can be achieved by replacing a promoter for any of the rfb genes that are needed for synthesis of the LPS O-antigen with the $araCP_{BAD}$ activator-repressor-promoter system. There is thus no reason to believe that one of ordinary skill in the art would doubt that the Applicant was in possession of various means for regulating synthesis of LPS O-antigens as currently claimed.

C) Applicants state with respect to item iii) (i.e. that the specification fails to disclose how to determine what constitutes first carbohydrate antigen capable of ceasing synthesis in vivo and exposing a second carbohydrate antigen), Applicant first notes that the claims as currently amended recite: a) "an LPS O-antigen" rather than "a first carbohydrate antigen" and "exposing an LPS core oligosaccharide antigen" rather than "a second carbohydrate antigen". At the time of filing, those skilled in the art would recognize what constitutes "an LPS-O antigen" and what constitutes "an LPS core oligosaccharide". For example, the discussion of these bacterial antigens spanning pages 2 and 3 of the specification as originally filed amply demonstrates that those skilled in the art would recognize the identity of these elements of the claims as currently amended.

Examiners Response to Applicants Arguments:

With regard to Points (A), (B), and (C), the instant claims are drawn to a live attenuated strain of *Salmonella* comprising (a) a regulatable $araCP_{BAD}$ promoter that is operably linked to a fur gene, wherein said fur gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non- expression of said fur gene in vivo causes synthesis of iron regulated outermembrane proteins (IROMP) and (b) a means for regulatable synthesis an LPS-O-antigen, wherein said LPS O-antigen ceases to be synthesized in vivo, exposing an LPS

core oligosaccharide antigen that is conserved among *Salmonella* species and *E. coli* strains; wherein said attenuated strain has enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains. Therefore Applicant must adequately describe the claimed genus of LPS O-antigens capable of being conserved among all *Salmonella species and E. coli* strains and capable of enhancing the ability to induce cross protective immunity against *Salmonella* species and *E. coli* strains in an attenuated strain. The specification is limited to *OMP and IROMP* antigens conserved among *Salmonella species and E. coli* strains that are capable of being synthesized caused by non-expression of an iron regulatory protein from fur gene *in vivo* and limited to LPS-O antigens conserved among *Salmonella species and E. coli* strains capable of ceasing synthesis *in vivo*. The limited number of species disclosed in the specification is not deemed to be representative of the genus of the LPS O-antigens encompassed by the instant claims. Moreover, Applicant is reminded that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. Therefore, the specification is silent to which LPS O-antigens are capable of being conserved among *Salmonella* species and *E. coli* strains in an attenuated strain with enhanced ability to induce cross protective immunity against *Salmonella* species and *E. coli* strains. Moreover, Applicant has not shown the correlation between structure and function as it applies to the claimed genus LPS O-antigens. Thus, applicant was not in possession of the claimed genus. The LPS O-antigens cited by applicant as being effective in an attenuated strain that has enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains are not representative of the claimed genus. Hence applicant's arguments are unpersuasive.

As outlined previously, the claims are drawn to a vast genus of LPS O-antigens. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members

from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention.

Applicants must adequately describe the genus of LPS O-antigens capable of being conserved among all *Salmonella species and E. coli* strains and capable of enhancing the ability to induce cross protective immunity against *Salmonella* species and *E. coli* strains in an attenuated strain.

Applicants have only disclosed the following. The specification discloses bacterial strains that produce the group B LPS O-antigen side chains using slide agglutination assays within antisera resulting in moderate and high agglutination (see Table 4 pg. 33). The specification discloses a *Salmonella typhimurium* (*S. typhimurium)* strain χ8650 which demonstrates a function of time or number of generations of growth in nutrient broth medium in the absence of added mannose is a gradual loss of LPS O-antigen side chains (see pg. 33 second paragraph). Applicants disclose the administration of the *S. typhimurium* strain χ8650 to mice and further observe the morbidity and mortality for 30 days, wherein the survivors from said strain were challenged with virulent wild-type *S. typhimurium UK-1* χ3761 strain (see pg. 37), wherein the *S. typhimurium* strain χ8650 is grown in a nutrient broth medium in the absence of added mannose which indicates a gradual loss of LPS O-antigen side chains that are reproduced *in vivo* in said strain after immunization of an animal host, enters visceral tissue. Applicants have disclosed the administration of *S. typhimurium* χ8754 strain and further challenge with virulent wild-type *Salmonella enteritidis* χ3700 strain (see pgs. 40-42), wherein the survivors from the challenge induced IgG antibodies to *Salmonella and Escherichia coli (E. coli)* outer membrane proteins *(OMPs)* and iron-regulated outer membrane proteins *(IROMPs)* (see pgs. 41-42). Therefore the specification is limited to *OMP and IROMP* antigens conserved among *Salmonella species and E. coli* strains that are capable of being synthesized caused by non-expression of an iron regulatory protein from fur gene *in vivo* and limited to LPS-O antigens conserved among *Salmonella species and E. coli* strains capable of ceasing synthesis *in vivo.* The limited number of species disclosed in the specification is not deemed to be representative of the genus of the LPS O-antigens encompassed by the instant claims. Moreover, Applicant is reminded that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606

(CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. Therefore, the specification is silent to which LPS O-antigens are capable being conserved among all *Salmonella species and E. coli* strains and capable of enhancing the ability to induce cross protective immunity against *Salmonella* species and *E. coli* strains in an attenuated strain. Moreover, Applicant has not shown the correlation between structure and function as it applies to the claimed genus LPS O-antigens. Thus, the LPS O-antigens cited by applicant as being effective in an attenuated strain that has enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains are not representative of the claimed genus.

The specification, does not disclose distinguishing and identifying features of a representative member of the genus of LPS O-antigens as to which the claims are drawn, such as a correlation between the structure of LPS O-antigens and its recited functions capable being conserved among all *Salmonella species and E. coli* strains and capable of enhancing the ability to induce cross protective immunity against *Salmonella* species and *E. coli* strains in an attenuated strain, so that the skilled artisan could immediately envision or recognize at least a substantial number of members of the claimed genus of LPS O-antigens. **Moreover, Applicant has not demonstrated any LPS O-antigen capable being conserved among all *Salmonella species and E. coli* strains and capable of enhancing the ability to induce cross protective immunity against *Salmonella* species and *E. coli* strains in an attenuated strain.** Therefore, the specification lacks written description of the instant claimed invention. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of regulators as to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus aforementioned above.

MPEP § 2163.02 states, "an objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. See Vas-Cath, Ink's. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "'Written Description" Requirement (66 FR 1099-1111, January 5,2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104).

The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

Therefore, absent a detailed and particular description of a representative number of the members of the genus of LPS O-antigens, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of LPS O-antigens with the recited activities. Therefore, in accordance with the *Guidelines*, the description of any regulator is not deemed representative of the genus of regulators to which the claims refer and therefore the claimed invention is not properly disclosed.

Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Enablement

6. The rejection of 1-2, 9-10, 21, 26, and 31-32 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in the previous Office Action. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants arguments filed in response to the 35 U.S.C. 112 first paragraph, March 29, 2010 is carefully considered, but not found to be persuasive for the reasons below.

Applicant arguments:

A) Considering the relevant Wands factors of guidance of the specification/existence of working examples, the Office argued that the specification was "devoid of any teaching that the claimed prevents Salmonella and E. coli infection" and that one skilled in the art "would not accept on its face the examples given in the specification as being correlative or representative of

a successful model". First, all of the claims under consideration by the Office are drawn to a "live attenuated strain of Salmonella". The Applicant demonstrates in Example 6 (see pages 40-41, see Table 7) that mice inoculated with an exemplary live attenuated strain (Δpmi-2426ΔPfur223::TT araCP$_{BAD}$) exhibit 80-100% survivorship following a challenge dose of virulent wild-type Salmonella that is two orders of magnitude (i.e. 1x10^9) greater than the challenge dose of wild type virulent Salmonella (i.e. 1 x10^7) that results in 0% survivorship in control mice that are not inoculated with the exemplary live attenuated strain. The Applicant further demonstrates in Example 7 (see pages 41-42, see Table 8) that mice inoculated with an exemplary live attenuated strain exhibit a dose dependent increase of up to 80% survivorship following a challenge dose of a second and distinct virulent wild-type Salmonella that results in 0% survivorship in control mice that are not inoculated with the exemplary live attenuated strain. The Applicant also demonstrates in Example 8 (pages 42-43) and the associated figures 11 and 12 that mice inoculated with the exemplary live attenuated strain exhibit substantial antibody responses to the OMPs and IROMPs from a wide variety of Salmonella and E. coli strains. The observed antibody responses to IROMPs from a wide variety of Salmonella and E. coli strains is especially significant in that contemporaneous art teaches that antibodies directed against IROMPs can provide some degree of immuno-protection (see Bolin et al. Infect. Immun. 55(5), 1239, 1987, referred to by the Office on Page 12 of the response) and thus weighs in favor of enablement. Applicant therefore respectfully disagrees with the Office's statement that "(t)he working examples do not disclose any empirical data or results indicative of a preventing Salmonella and E. coli infection as claimed".

B) Applicant also respectfully reminds the Office that it "must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example" and that "a rigorous or an invariable exact correlation is not required" (see MPEP §2164.02, citing Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)). Although the Office states that "the data fails to show...vaccine protection", the Examples cited above appear to show just that (i.e. that mice inoculated with the invention as claimed survive a Salmonella challenge whereas inoculated control mice perish following the Salmonella challenge). The Office is therefore respectfully requested to provide such reasons to support the alleged "lack of correlation" in the event that the Office maintains the rejections of claims for an alleged lack of

enablement. Furthermore, Applicant respectfully requests that the Office provide some basis for the allegation "that one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model" (page 12 of the Office Action).

C) The Office is respectfully directed to the publication in a peer reviewed scientific journal in 1987 (see Curtiss and Kelly, Infect. Immun. 55(12):3035, 1987, provided herewith in an accompanying IDS) where substantially similar experiments are used to demonstrate the effectiveness of oral immunization with avirulent Salmonella (see Table 7, pg. 3041 and related paragraph on pg. 3040). The Office is also respectfully directed to a more recent 2009 publication in that same peer reviewed scientific journal (see Curtiss et al, Infect. Immun. 77(3): 1071, 2009, provided herewith in an accompanying IDS) where substantially similar experiments are used to demonstrate induction of protective immunity with attenuated Salmonella strains (see Table 7, pg. 3041 and related paragraph on pg. 3040). Based on these two publications in a peer reviewed scientific journal, it is evident that those skilled in the art in fact accepted the types of experiments presented by the Applicant as being correlative both in 1987 and in 2009. Applicant further notes that the Office also relies on an article published in 1987 in this same peer reviewed scientific journal as being representative of the "state of the art" (see Bolin et al. Infection and Immunity 1987 reference cited by the Office on Page 12 of the Office Action). Bolin et al. (Infect. Immun. 55(5), 1239, 1987) and Sood et al. (Mol Cell Biochem. 273(1-2):69, 2005) disclose passive immunization of subjects with an antibody raised against IROMPs whereas the Applicant's invention is directed to live attenuated strains of Salmonella that induce production of antibodies in an inoculated host organism. Sood et al. additionally disclose in the Abstract of their publication that mice that were actively immunized with IROMPs were protected against challenge by the pathogen. One skilled in the art would expect a much more robust immuno-protection would be obtained in a host inoculated with a live attenuated strain that can elicit a sustained host immune response than would be obtained in a host passively immunized with an antibody that would eventually be cleared from the host. Even in spite of this very critical difference between the Applicant's live attenuated strains and the experiments described in the cited references, that both Bolin et al. and Sood et al. in fact observed a certain level of protection by passive immunization with antibodies against IROMPs thus indicates that IROMPs

are effective antigens for inducing some level of protective immunity against Salmonella, indicating that the pending claims were enabled.

D) The references provided by the Office indicate that IROMPs apparently fall in that subset of antigens that result in a certain level of a protective response to infection, again indicating that the pending claims were enabled. The Office also cites the Greenspan et al. reference (Nature Biotechnology 17 (10):936, 1999) that speaks to the difficulty of defining immuno-epitopes and argues that immuno-epitopes that elicit a protective immuno-response can only be identified empirically. Again, the difficulties referred to in Greenspan et al. and by the Office are pertinent to compositions (i.e. protein epitopes) that are very different than the live attenuated strains provided by the Applicant that present a variety of outer membrane proteins (including LPS core oligosaccharide antigen and IROMPs) on their surface in an intact form where all accessible epitopes of those proteins are present. The Applicant's compositions thus do not rely on nor require identification of a single epitope of a single antigen as described in Greenspan et al. to elicit a protective response but rather present a series of antigens (including LPS core oligosaccharide antigen and IROMPs) in a form where multiple epitopes of each of those antigens are presented. Consequently, whatever unpredictability is associated with immunogenic protein epitope compositions of Greenspan et al. is not relevant to the live attenuated strains as claimed by the Applicant that do not rely on epitope predictions or use of a single epitope. As pointed out previously, the state of the art was such that there was an indication that one of the antigens (i.e. IROMPs) presented by the live attenuated derivatives can in and of itself provides a certain level of protective immunity, indicating that the pending claims were enabled. Furthermore, in the Applicant's case, there are working examples that demonstrate that the live attenuated strains as claimed actually provide protection to mice challenged with virulent Salmonella.

Examiners Response to Applicants Arguments:

With regard to Point (A), Applicants working examples 7 and 8 aforementioned is unpersuasive because the instant claims are drawn to a live attenuated strain of *Salmonella*, wherein said attenuated strain has enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains. The claims encompassing any LPS O-antigen conserved among all *Salmonella* species and E. coli strains that has enhanced ability to induce cross-

protective immunity against any *Salmonella* species **and** *E. coli* strains in an attenuated strain is overly broad. Applicants have only shown mice inoculated with an exemplary live attenuated strain (Δpmi-2426ΔPfur223::TT araCP$_{BAD}$) exhibit 80-100% survivorship following a challenge dose of virulent wild-type Salmonella that is two orders of magnitude (i.e. $1X10^9$) greater than the challenge dose of wild type virulent Salmonella (i.e. $1 X10^7$) that results in 0% survivorship in control mice that are not inoculated with the exemplary live attenuated strain but not cross protection immunity against all *Salmonella* species and *E. coli* strains. Therefore the specification is limited to *OMP and IROMP* antigens conserved among *Salmonella species and E. coli* strains that are capable of being synthesized caused by non-expression of an iron regulatory protein from fur gene *in vivo* and limited to LPS-O antigens conserved among *Salmonella species and E. coli* strains capable of ceasing synthesis *in vivo*. The specification is also limited to antibody responses to IROMPs from a wide variety of Salmonella and E. coli strains. Furthermore, the exhibit 80-100% survivorship and antibody response does not indicate prevention (i.e. vaccine). Therefore as stated in the previous office action a vaccine by definition must provide protection against an infection demonstrable by challenge experiments. Consequently, Applicants have only shown examples that demonstrate an increase in survivorship not protection using specifically *Salmonella typhimurium* ΔPfur223::TTaraCP$_{BAD}$*fur* Δpmi-2426 strain. Therefore Applicant have only contemplated that any live attenuated strain of *Salmonella* species, wherein said attenuated derivative has enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains.

With regard to Point (B) Moreover, the working examples do not disclose any empirical data or results indicative of a vaccine, therefore, one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model. In regards to Applicants argument that the Examiner has not provided any specific evidence to suggest that the presently-claimed vaccine would not work, the Examiner has discussed the complexity of the vaccine art in the previous Office Action, therefore empirical data and or results from working examples indicative of a vaccine aforementioned above by definition would determine the success of the claimed invention. Therefore Applicants response is unpersuasive.

With regard to Points (C) and (D), in response to the reference Bolin et al and Sood et al (see Bolin et al. Infection and Immunity 1987 reference cited by the Office on Page 12 of the

Office Action). Bolin et al. (Infect. Immun. 55(5), 1239, 1987) and Sood et al. (Mol Cell Biochem. 273(1-2):69, 2005) cited by Applicants is unpersuasive because the claims are specifically limited to prevention not passive immunization of subjects with an antibody raised against IROMPS. The instant claims are drawn to a live attenuated strain of *Salmonella* comprising (a) a regulatable $araCP_{BAD}$ promoter that is operably linked to a fur gene, wherein said fur gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non- expression of said fur gene in vivo causes synthesis of iron regulated outermembrane proteins (IROMP) and (b) a means for regulatable synthesis an LPS-O-antigen, wherein said LPS O-antigen ceases to be synthesized in vivo, exposing an LPS core oligosaccharide antigen that is conserved among *Salmonella* species and *E. coli* strains; wherein said attenuated strain has enhanced ability to induce cross-protective immunity against *Salmonella* species **and** *E. coli* strains. The claimed invention encompasses cross-protective immunity (i.e. prevention which is correlated to a vaccine) with any LPS O-antigen conserved among all *Salmonella* species and E. coli strains that has enhanced ability to induce cross-protective immunity against any *Salmonella* species and *E. coli* strains in an attenuated strain. Therefore as stated in the previous office action a vaccine by definition must provide protection against any type of *Salmonella* and *E. coli* infection demonstrable by challenge experiments. Consequently, Applicants have only shown examples that demonstrate an increase in survival against specific bacteria not protection. As stated in the previous office action, the state of the art has limitations and is unpredictable with regard to said attenuated strain with enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains. Therefore, the references provided by the Office indicate that IROMPs do not result in a certain level of a protective response to infection.

As outlined previously, while being enabling for a *Salmonella typhimurium* ΔPfur223::TT$araCP_{BAD}$*fur* Δpmi-2426 strain comprising (a) a means for regulatable expression of a fur gene that encodes an iron regulatory protein, wherein said $araCP_{BAD}$ regulatable promoter is operably linked to said gene, wherein said gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non-expression of said

iron regulatory protein *in vivo* causes synthesis of an antigen of outer membrane protein (OMP) or iron outer membrane protein (IROMP) that is conserved among *Salmonella* species and E. coli strains, wherein said strain enhances the survival of an infection against *Salmonella* species and *E. coli* strains does not provide enablement for a live attenuated strain of *Salmonella* with enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains comprising (a) a regulatable $araCP_{BAD}$ promoter that is operably linked to a fur gene, wherein said fur gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non-expression of said fur gene in vivo causes synthesis of iron regulated outermembrane proteins (IROMP) and (b) a means for regulatable synthesis an LPS-O-antigen, wherein said LPS O-antigen ceases to be synthesized in vivo, exposing an LPS core oligosaccharide antigen that is conserved among *Salmonella* species and *E. coli* strains.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

(A) The nature of the invention;

(B) The breadth of the claims;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention

The instant claims are drawn to a live attenuated strain of *Salmonella* comprising (a) a regulatable $araCP_{BAD}$ promoter that is operably linked to a fur gene, wherein said fur gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is

not expressed when said attenuated strain is within internal tissues of an individual and wherein non- expression of said fur gene in vivo causes synthesis of iron regulated outermembrane proteins (IROMP) and (b) a means for regulatable synthesis an LPS-O-antigen, wherein said LPS O-antigen ceases to be synthesized in vivo, exposing an LPS core oligosaccharide antigen that is conserved among *Salmonella* species and *E. coli* strains; wherein said attenuated strain has enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains. ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains.

Breadth of the claims

The claims are overly broad. The claims encompass any live attenuated strain of any pathogenic *Salmonella* species comprising (a) a regulatable $araCP_{BAD}$ promoter that is operably linked to a fur gene, wherein said fur gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non- expression of said fur gene in vivo causes synthesis of iron regulated outermembrane proteins (IROMP) and (b) a means for regulatable synthesis an LPS-O-antigen, wherein said LPS O-antigen ceases to be synthesized in vivo, exposing an LPS core oligosaccharide antigen that is conserved among *Salmonella* species and E. coli strains, wherein said attenuated derivative has enhanced ability to induce cross-protective immunity against any *Salmonella* species and *E. coli* strains.

Guidance of the specification/The existence of working examples:

Applicants have only disclosed the following. The specification discloses bacterial strains that produce the group B LPS O-antigen side chains using slide agglutination assays within antisera resulting in moderate and high agglutination (see Table 4 pg. 33). The specification discloses a *Salmonella typhimurium* (*S. typhimurium)* strain χ8650 which demonstrates a function of time or number of generations of growth in nutrient broth medium in the absence of added mannose is a gradual loss of LPS O-antigen side chains (see pg. 33 second paragraph). Applicants disclose the administration of the *S. typhimurium* strain χ8650 to mice and further observe the morbidity and mortality for 30 days, wherein the survivors from said strain were

challenged with virulent wild-type *S. typhimurium UK-1* χ3761 strain (see pg. 37), wherein the *S. typhimurium* strain χ8650 is grown in a nutrient broth medium in the absence of added mannose which indicates a gradual loss of LPS O-antigen side chains that are reproduced *in vivo* in said strain after immunization of an animal host, enters visceral tissue. Applicants have disclosed the administration of *S. typhimurium* χ8754 strain and further challenge with virulent wild-type *Salmonella enteritidis* χ3700 strain (see pgs. 40-42), wherein the survivors from the challenge induced IgG antibodies to *Salmonella and Escherichia coli (E. coli) OMPs and IROMPs* (see pgs. 41-42). Therefore the specification is limited the survival of mice through the administration of *Salmonella typhimurium* ΔPfur223::TTaraCP$_{BAD}$*fur* Δpmi-2426 strain. The claimed invention is drawn to cross-protective immunity against *Salmonella* species *and E. coli* strains and as a result cross-protective immunity is correlated to a vaccine. A vaccine by definition must provide protection against an infection demonstrable by challenge experiments. The data as set forth supra does not demonstrate that the live attenuated derivative aforementioned above confers "protection" against infection by *Salmonella* species *and E. coli* strains. The data merely shows that said attenuated strain increases the number of mice that survived from *Salmonella and E. coli* infection. Therefore the data fails to show or vaccine protection against *Salmonella* species *and E. coli* strains. Therefore, one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model. The working examples do not disclose any empirical data or results indicative of a preventing *Salmonella and E. coli* infection as claimed. The specification is devoid of any teaching that the claimed prevents *Salmonella and E. coli* infection.

State of the art

The art discloses turkeys passively immunized with antibody against IROMPs of *E. coli* which significantly reduced the growth of bacteremia and the recovery of *E. coli* from air sacs thus increasing the survival of turkeys (see abstract and pg. 1242 specifically and Bolin et al 1987 Infection and Immunity pgs. 1239-1242 in its entirety). The art discloses mice passively immunized with antibody against IROMPs of *Salmonella enterica serovar Typhi* which significantly reduced the growth of bacteremia and increase the survival of mice and indicates that anti IROMPs antibodies may play an important role in providing protection at a systemic

and mucosal level (see abstract and pgs. 69-71 and pg. 74 and Sood et al 2005 Molecular and Cellular Biochemistry Vol. 273 pgs. 69-78 in its entirety). Although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from infection (Chandrasekhar et al., US Patent 6,248,329, col. 1, and lines 35-41). It is well recognized in the vaccine art, that it is unclear whether an antigen derived from a pathogen will elicit protective immunity. Ellis (Chapter 29 of Vaccines, Plotkin, et al. (eds) WB Saunders, Philadelphia, 1998, especially p. 571, paragraph 2) exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.., and thus protect the host against attack by the pathogen." As evidenced by Greenspan et al. (*Nature Biotechnology* 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. For the reasons set forth supra, the state of the art is has limitations to said derivative aforementioned above and the state of the art is unpredictable with regard to said derivative with enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains.

In conclusion, the claimed invention is not enabled for a live attenuated strain of *Salmonella* with enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains comprising (a) a regulatable $araCP_{BAD}$ promoter that is operably linked to a fur gene, wherein said fur gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non-expression of said fur gene in vivo causes synthesis of

iron regulated outermembrane proteins (IROMP) and (b) a means for regulatable synthesis an LPS-O-antigen, wherein said LPS O-antigen ceases to be synthesized in vivo, exposing an LPS core oligosaccharide antigen that is conserved among *Salmonella* species and *E. coli* strains. Furthermore, the claims encompassing any live attenuated strain of any pathogenic *Salmonella* species comprising any LPS O-antigen conserved among *Salmonella* species and *E. coli* strains which has enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains is overly broad. The specification fails to teach that said attenuated strain as set forth can produce a protective response in a host, for prevention of *Salmonella* and *E. coli* as is requisite of a vaccine. The state of the art teaches that there are limitations to a vaccine and the state of the art is unpredictable. In view of the lack of support in the art and specification for an effective vaccine, it would require undue experimentation on the part of the skilled artisan to make and use the vaccine as claimed; therefore the claims are not enabled. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed composition.

Conclusion

7. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be

reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina A Archie
Examiner
GAU 1645
REM 3B31

/Robert A. Zeman/
for Nina Archie, Examiner of Art Unit 1645